

Tissue Repair, Fibrosis, and Healing

HST.035

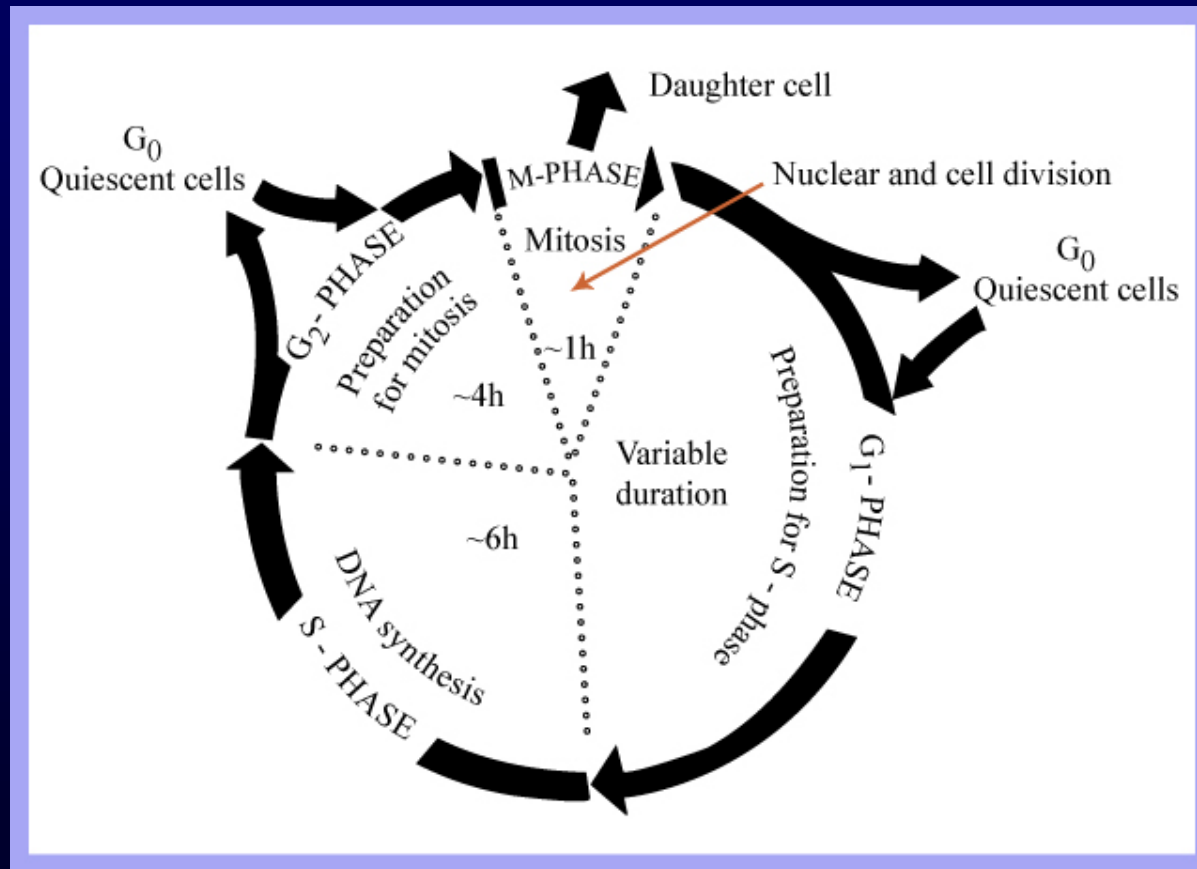
Spring 2003

Tissue Repair (Healing)

- Regeneration of injured tissue (replacement by normal cells of the same kind)
- Replacement by fibrous tissue (fibrosis, scarring)

Normal Cell Proliferation

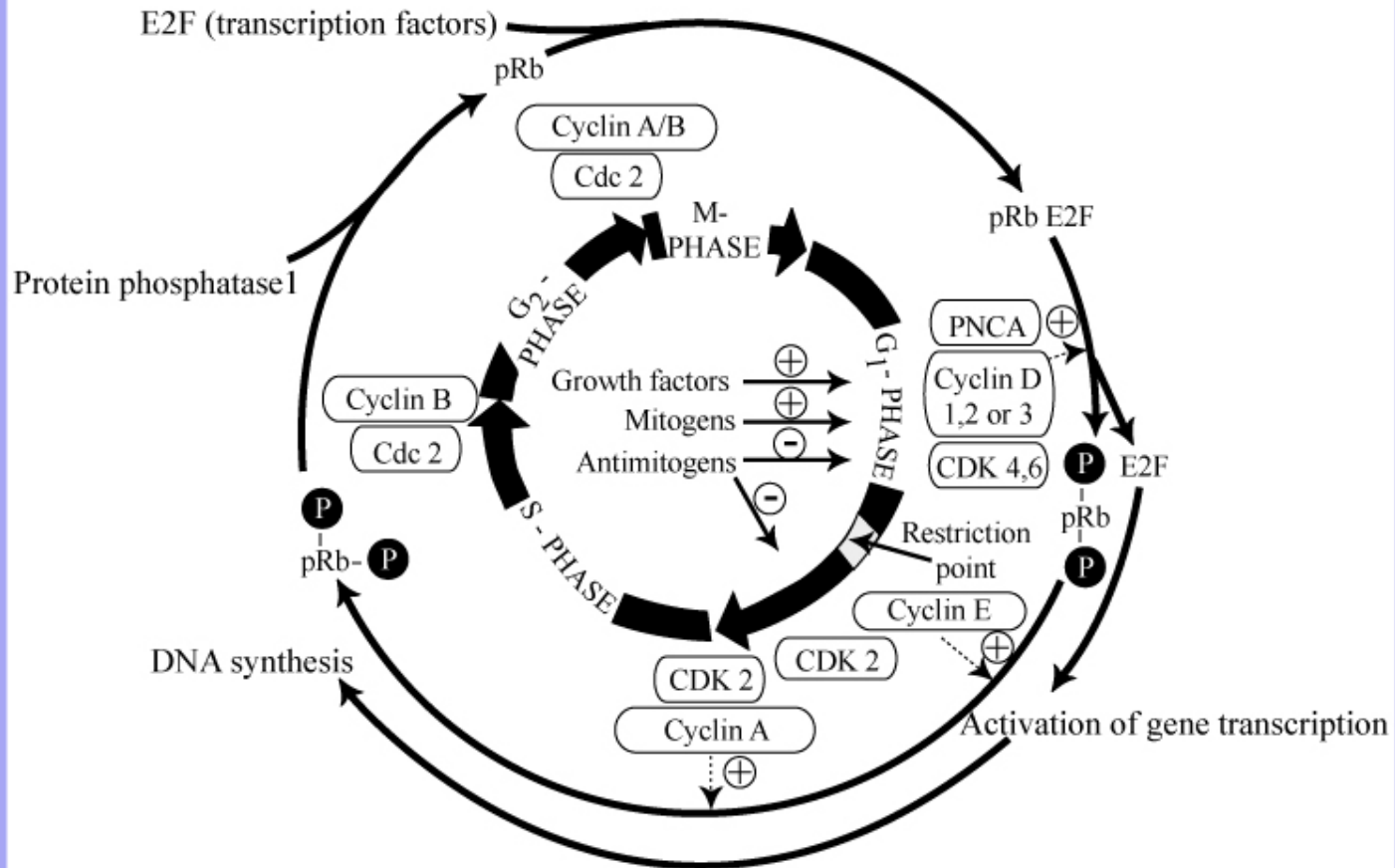
Proliferating cells progress through a series of defined phases and checkpoint, collectively call the *cell cycle*



Control of Cell Cycle

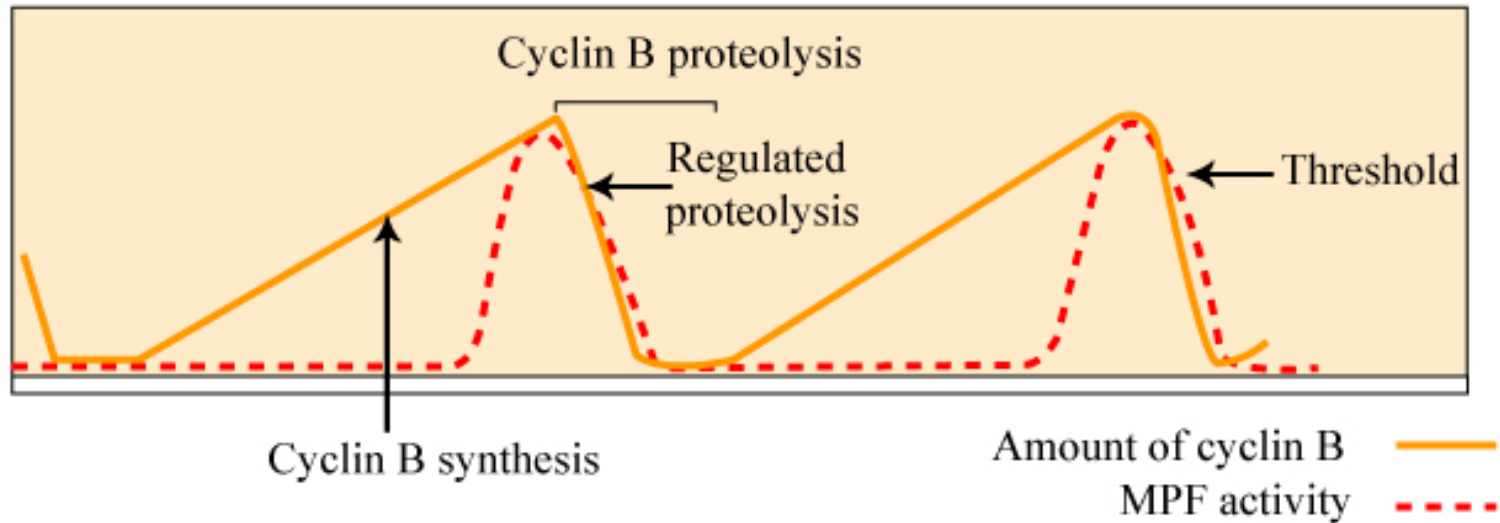
- Progression through the cell cycle is controlled at specific *checkpoints (restriction point in G_1 , mitosis entry and mitosis exit)*
- Transition between stages of mitosis is triggered by increased activity of *cyclin-dependent kinases (CDK)*
- Each CDK modulates the activity of a subset of cellular targets specific for progression through individual transitions with the cell cycle

Control of Cell Cycle



Control of Cell Cycle

CDK activity is controlled by constant synthesis and cyclic breakdown of specific *cyclins*



Control of Cell Cycle

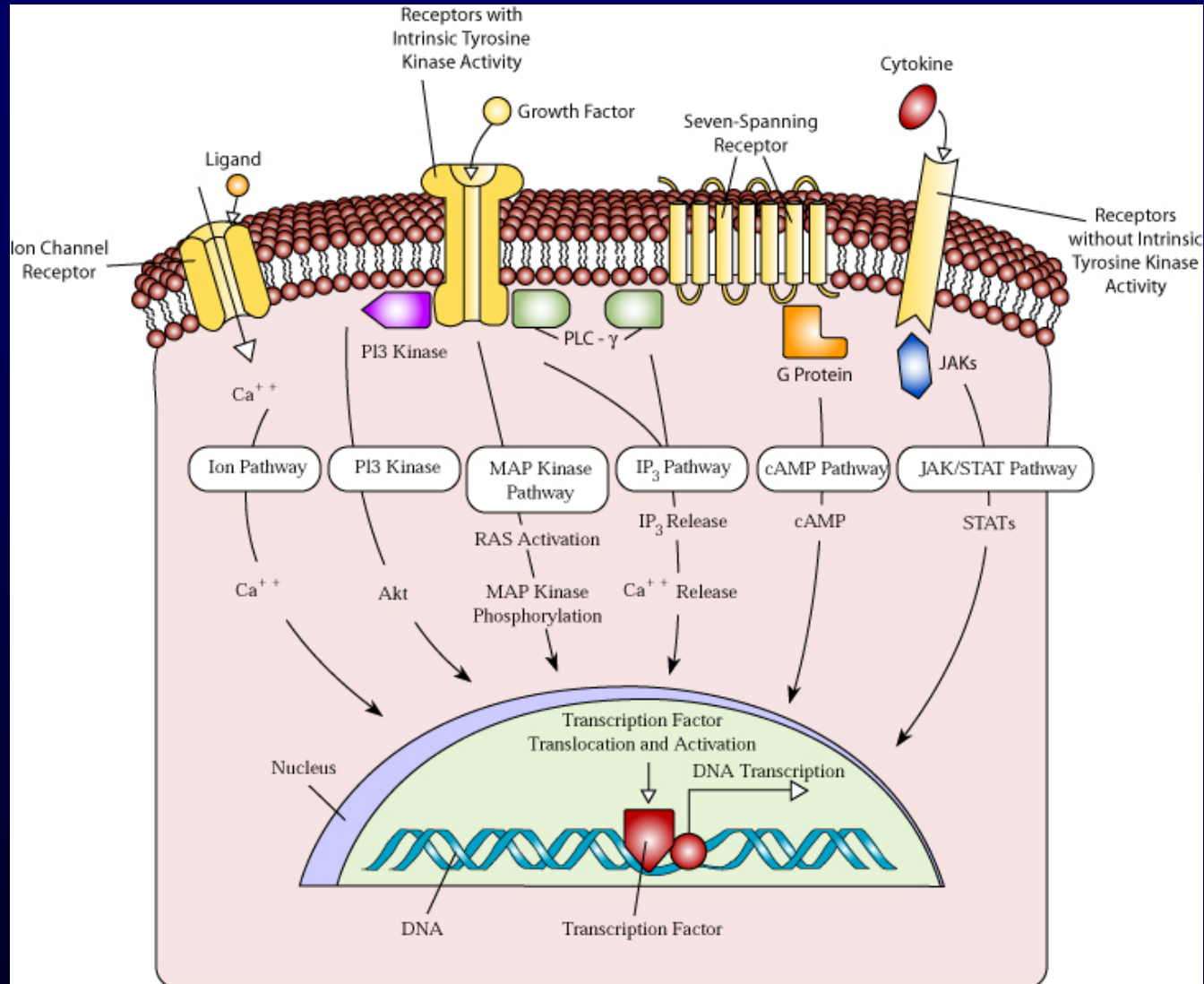
- Cyclin-CDK complexes are also regulated by the binding of *CDK-inhibitors*
- CDK-inhibitors are particularly critical at at $G_1 \rightarrow S$ and $G_2 \rightarrow M$ checkpoints, at which time adequacy and fidelity of DNA synthesis and replication are monitored
- When DNA is found to be damaged, TP53 (p53) is stabilized and induces transcription of CDKN1A (p21), an inhibitor which arrests cells in G_1 or G_2
- If DNA damage is too extensive, TP53 will initiate apoptosis

**Cell growth and differentiation are dependent
on extracellular signals from soluble
polypeptide growth factors and the ECM**

Polypeptide Growth Factors

- Soluble growth factors are transported either via the Gap junctions, or by autocrine, paracrine, endocrine, or synaptic transmission
- For intracellular receptors, ligand binding leads to formation of complexes that directly associate with nuclear DNA and activate transcription
- For cell surface receptors, ligands bind to a variety of receptor types that ultimately lead to activation of nuclear transcription factors

Major Types of Cell Surface Receptors



ECM: Interstitial Matrix and Basement Membrane

Please see Kumar et al. *Robbins Basic Pathology*. 7th edition. WB Saunders 2003. ISBN: 0721692745.

Biological Roles of the ECM

- Mechanical support
- Determination of cell polarity
- Control of cell growth
- Control/maintenance of cell differentiation
- Scaffolding for tissue renewal
- Establishment of tissue microenvironment
- Storage and presentation of regulatory proteins

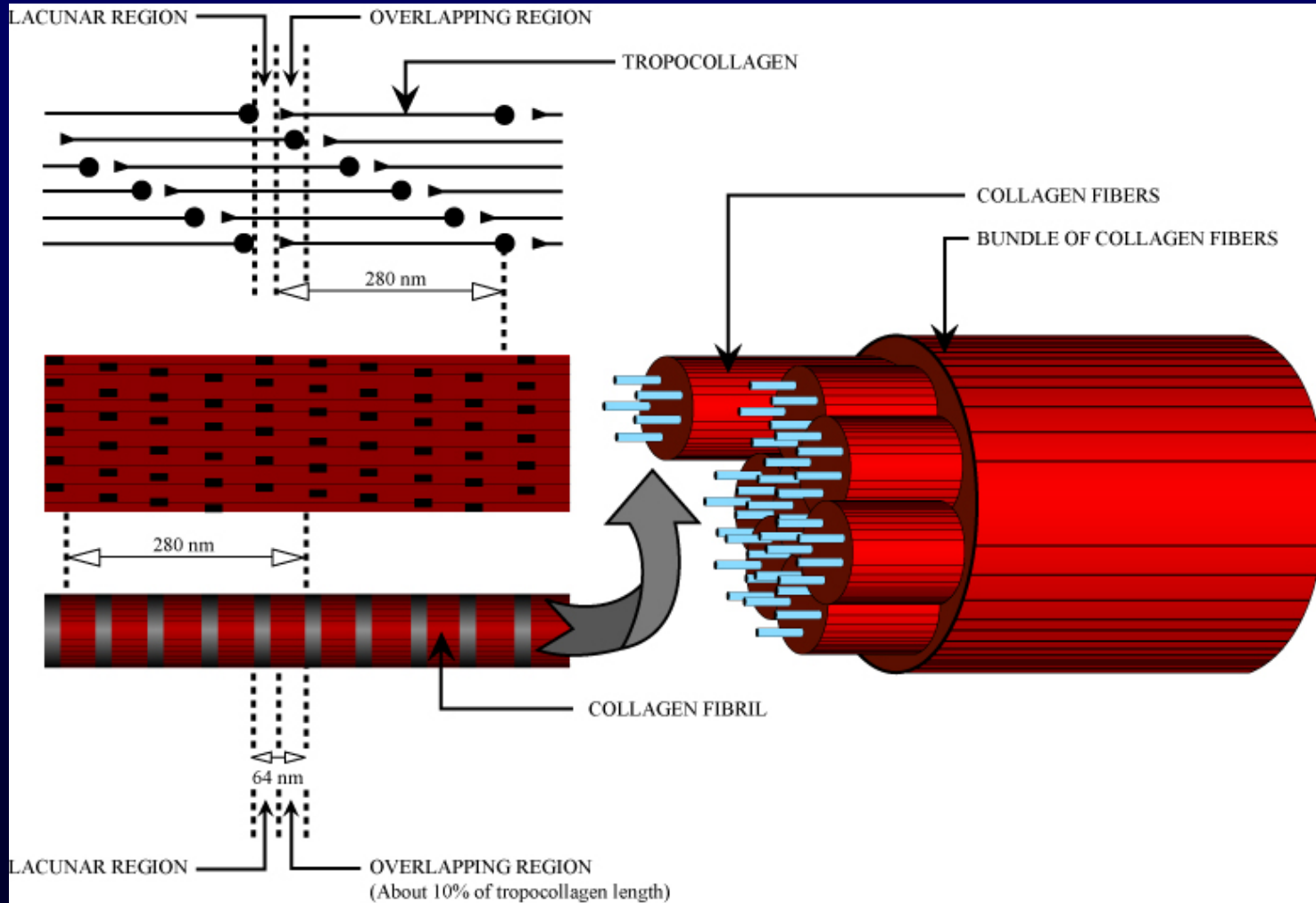
Major Components of the ECM

- Collagen
- Elastic fibers
- Proteoglycans and hyaluronan
- Fibronectin
- Laminin
- Integrins

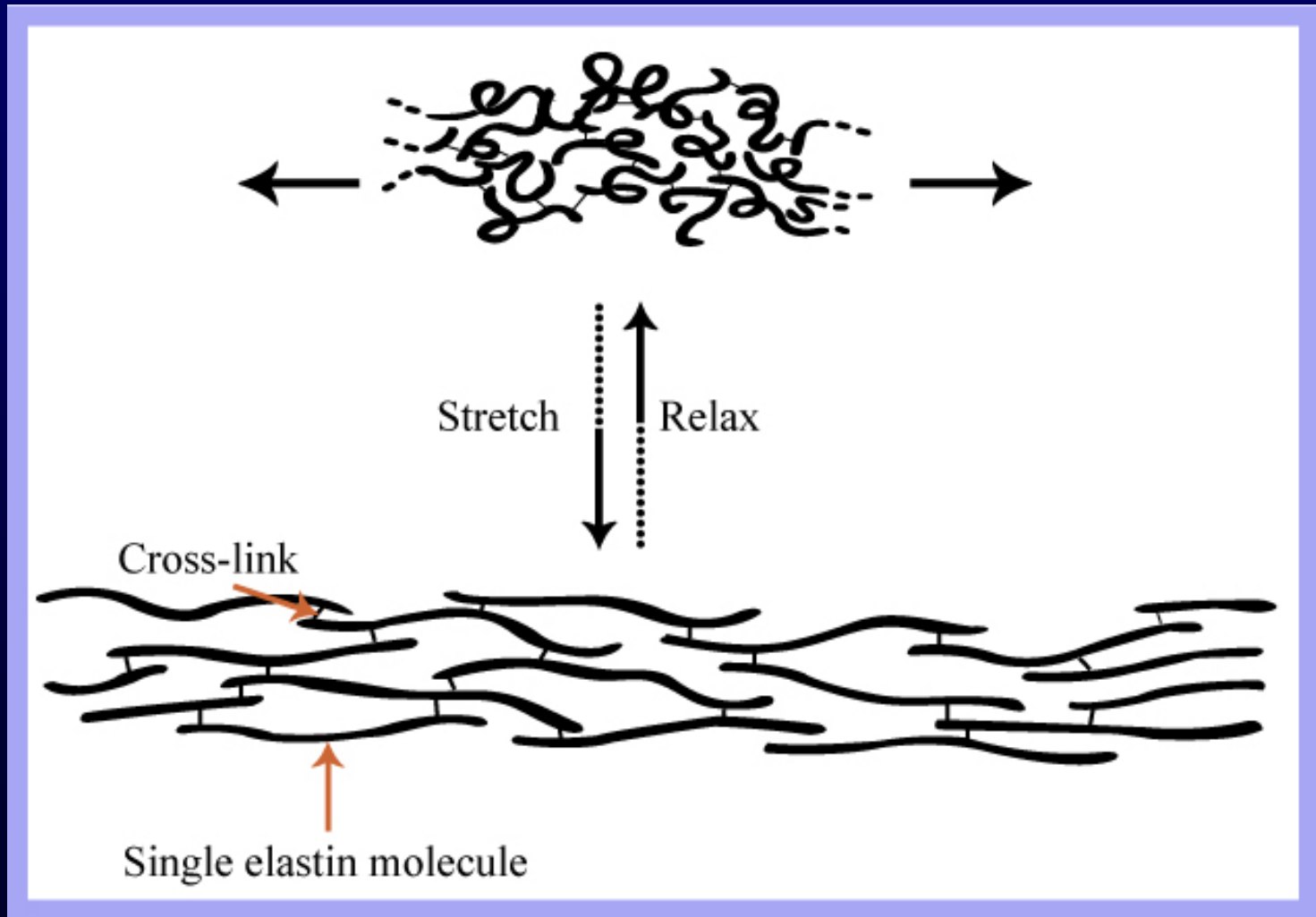
Fibrillar Collagen: Tensile Strength

Please see figures 5-17 and 5-18 of Junqueira & Carneiro. *Basic Histology: Text and Atlas*. 10th edition. McGraw Hill. 2003. ISBN: 0071378294.

Collagen Fibrills



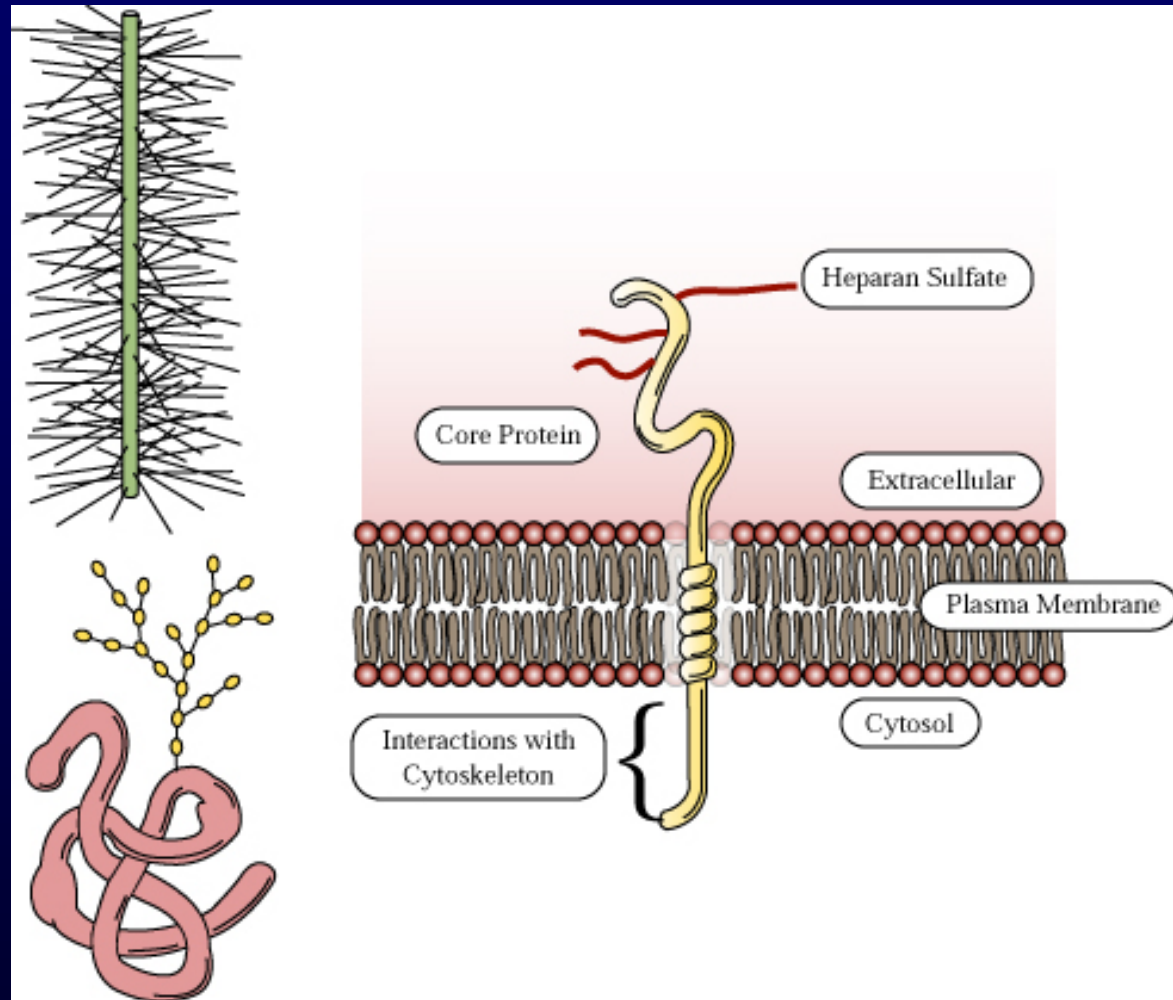
Elastic Fibers: Stretch and Recoil



Proteoglycans and Hyaluronan: Hydrated Gels

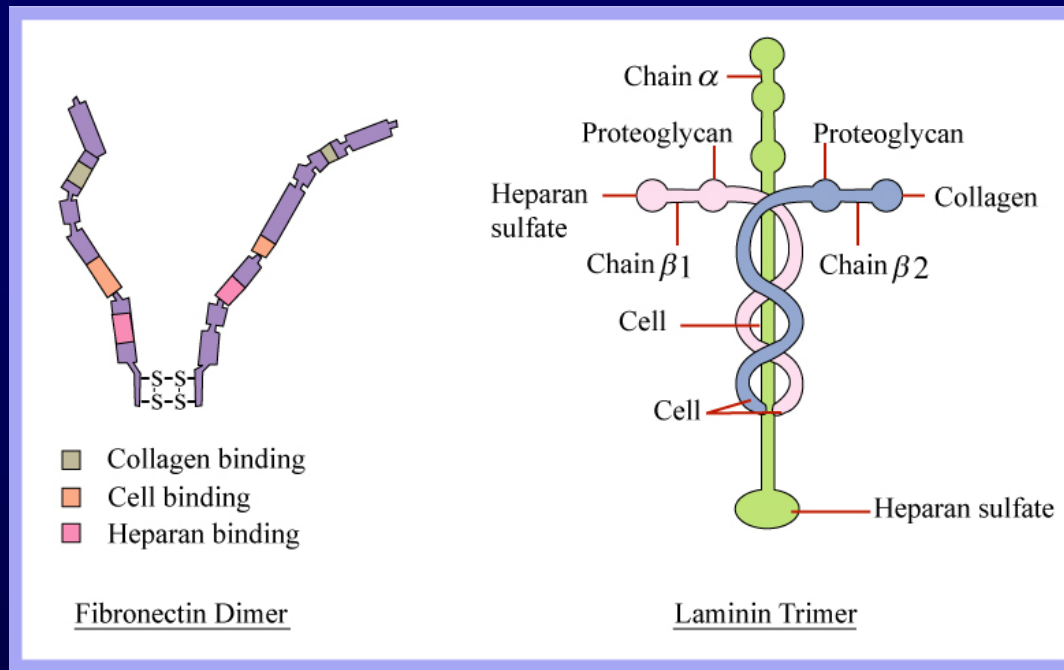
Proteoglycans have a core of protein to which glycosaminoglycans are attached

Glycoproteins are globular proteins with branched monosaccharide chains



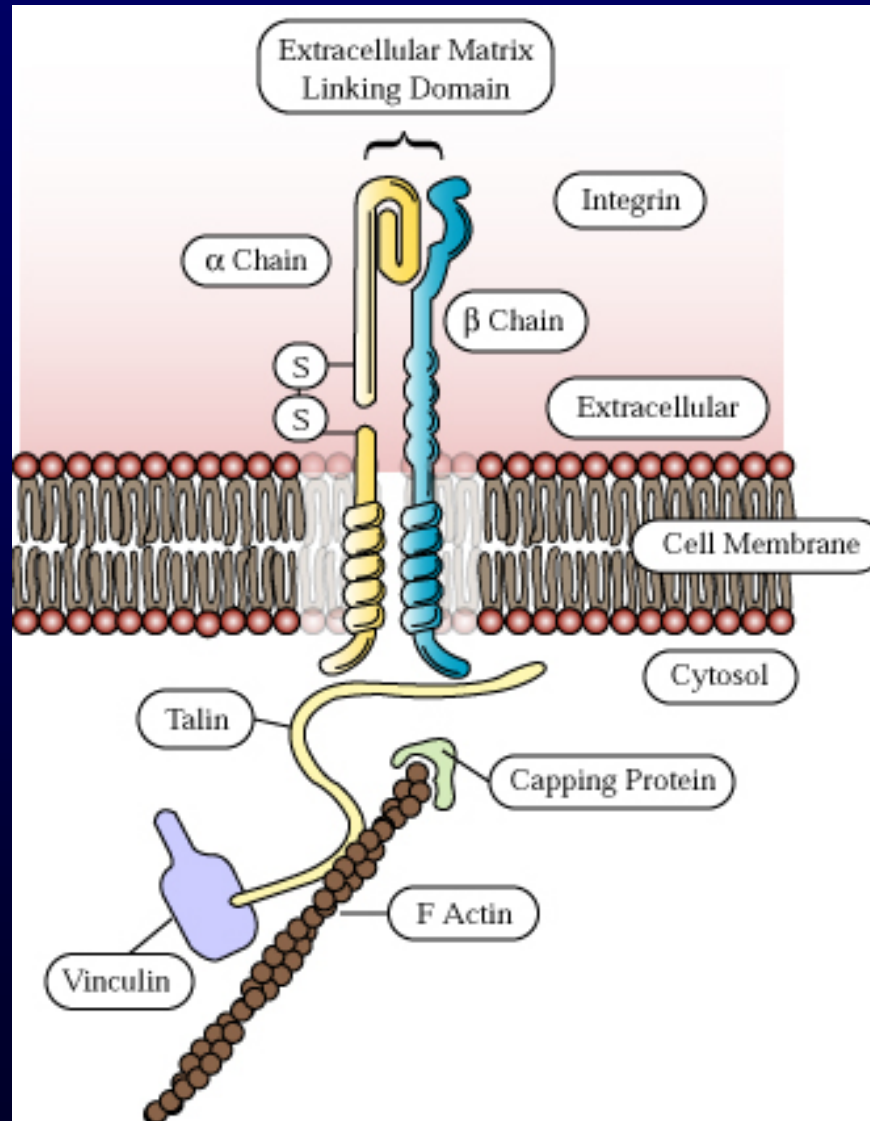
Proteoglycans such as syndecan can be transmembrane proteins with ligand binding capacity

Fibronectin and Laminin



- Fibronectin bind to a wide spectrum of ECM components and can attach to cell surface integrins
- Laminin is a key glycoprotein in the basement membrane that binds underlying ECM components such as type IV collagen
- Laminin also modulates cell survival, proliferation and differentiation

Integrins link the ECM to Actin Cytoskeleton through Focal Adhesion Complexes



ECM and Growth Control

Repair by Connective Tissue (Fibrosis/Scarring)

- Occurs when severe cell injury and damage to ECM framework precludes regeneration of native tissue
- Fibrosis progresses through four main stages:
 - Angiogenesis
 - Migration and proliferation of fibroblasts
 - Deposition of ECM
 - Remodeling of ECM

Fibrosis/Scarring

Please see figure 3-10 of Kumar et al. *Robbins Basic Pathology*. 7th edition. WB Saunders 2003. ISBN: 0721692745.

Overview of Tissue Response to Injury

